REMARKS

Claims 41 to 65 and 67 to 69 remain in the case.

Claims 41 and 67 have been amended in order to better define what the Applicant considers his invention, as fully supported by an enabling disclosure. In essence, the amendments to claims 41 and 67 rephrase the fact that the urine sample "does not contain semen". They previously recited "urine sample having not been obtained immediately following ejaculation". Such support can be found from the common and general definition of urine. Specific support is also found in paragraph 025 which relates to a general urine sample obtained without digital rectal examination (DRE), a urine sample obtained after DRE or "other types of samples such as sperm or mixed urine and sperm (e.g., first urine sample following ejaculation)". Applicant reiterates that the definition of "urine" as used in the present invention relates to regular urine samples ("having not been obtained following ejaculation"). This is clearly supported by the fact that sperm-containing samples are defined as "other types" of urine samples in the instant application.

REJECTIONS UNDER 35 U.S.C. § 103

The rejection of claims 41-50, 57, 58, 61-63, and 65-68 as being allegedly unpatentable over Bussemakers *et ai.,* (US 7,008,765 B1) in view of Clements *et ai.,* 1999 (1. Urol. 161: 1337-1343) under 35 U.S.C. § 103(a), has been nlaintained. Applicant traverses this rejection as follows.

As previously stated in our response of September 20, 2007, Applicant agrees with the Examiner that Bussemakers teaches "performing an RT-PCR RNA amplification assay on prostate biopsy sample" [our emphasis]. Applicant also stresses that by definition, a prostate biopsy sample should contain at least one prostate cell. At page 3, the Examiner states:

> "Bussemakers et al., further teaches a method COmprISIng (a) perfonning an RT-PCT RNA amplification assay on a prostate biopsy sample comprising at least one prostate cell of said patient..., (b) performing a second RT-PCR RNA amplification assay on said sample..., (c) detecting in said sample an amount of PCA3 and PSA mRNA; and (d) wherein an increased level of PCA3 mRNA, as compared to the level of PCA3 mRNA in a urine sample from a nonnal subject, indicates that said patient will develop prostate cancer or that said patient has prostate cancer; and (e) wherein an absence of PCA3 mRNA..." [our emphasis]

Applicant respectfully submits that the beginning of the citation from the Examiner on a prostate biopsy sample, and its conclusion concerning a urine sample, is incorrect. As alluded to earlier, while Bussemakers does teach detection of PCA3 from a biopsy sample, it certainly does not suggest that prostate cells present in a urine sample could be used to detect PCA3 mRNA in accordance with the present invention. Further, the Applicant respectfully disagrees with the Examiner concerning the allegation that "Bussemakers teaches a method wherein detection of PSA would validate a negative result for PCA3 detection". Applicant does not find such a teaching or suggestion. Indeed, it is respectfully submitted that since Bussemakers uses a prostate biopsy as a sample, which by definition contains numerous prostate cells, there would be no need for Bussemakers to detect PSA mRNA as an indicator of the presence of prostate cells in the sample. Of note, the tenn "urine" is found only once in Bussemakers, at column 24, line 26 in the context of an immunological assay.

At page 4, the Examiner alleges that Bussemakers teaches "a method wherein RNA is extracted using a target capture method (Example 2 in particular)". Applicant cannot see where in Example 2 (or elsewhere), such a teaching can be found.

In the middle of page 4, the Examiner states that "Bussemakers does not specifically teach methods using a urine sample, a voided urine sample from a patient having an increased number of prostate cells therein, a urine sample containing semen or a urine sample collected following a digital rectal exam". Applicant agrees with the Examiner and

directs the Examiner to the contradiction between this statement and that at the bottom of page 3 concerning the teaching of Bussemakers in urine.

Concerning "simultaneously", Applicant refers the Examiner to the response of September 20,2007, at page 18, first paragraph which comprises "the term 'simultaneously' is found only once in Bussemakers in the context of digesting the vector pMB9 with two restriction enzymes 'simultaneously'."

Turning to Clements, the Examiner alleges at page 4, that it teaches that PSA mRNA is a "selective marker of prostate cells" [our emphasis]. The Applicant will address this issue below, together with the allegations that "PSA is *exclusively* expressed in cells of the prostate" [emphasis in the original, at page 7, lines 11-12 of the OA].

Applicant agrees with the Examiner that Clements indeed teaches a method "using RT-PCR to detect prostate cells in urine containing semen" [our emphasis]. As argued in Applicant's previous response (at pages 19-20), the use of urine which does not contain semen is clearly not validated by Clements, as corroborated at page 1342, bottom left column when it is stated:

> "Since the result were comparable between ejaculate and urethral washings [defined as "the first urinary void immediately after masturbation"] from both groups of patients and control subjects, it is possible that urethral washings specimens could be used instead of ejaculate for this assessment in the future".

Thus, even for the urethral washings, which are post-ejaculation samples and thus contain sperm/semen, there is a doubt in Clements as to their value for diagnosis. It follows that Clements does not teach that a regular urine sample (e.g., a voided urine sample "not containing semen") is a suitable sample for the detection of the unstable RNA molecule.

With respect to support for the amended language, Applicant points out that MPEP's section 2173.05(i) discusses negative limitations. This section states (in part):

> "Any negative limitation of exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims."

In the present case, the definition of "biological sample" under paragraph [0073] affinnatively indicates that "sample" embraces "semen or other bodily fluids" in addition to urine. Thus, the negative limitation "not comprising semen" is supported by the original description and the guidance provided by the MPEP.

The Examiner also claims, in the penultimate paragraph of page 4, that Clements further "teaches methods using urine samples from patients that have had digital rectal exams (left column of page 1338, in particular)". It appears that the Examiner confuses the issue of massaging the prostate to increase the number of prostate cells in the urine sample collected after the DRE ["...preferably is a urine sample following digital rectal examination (or other means which increase the content of prostate cells in urine). " at paragraph 0073 of the application] with performing a DRE to assess the smoothness of the prostate and identify patients who should obtain a biopsy. Indeed, the samples of Clements were not obtained following digital rectal exams (DRE). The DRE served to recruit the patients in the study (page 1338, left column).

> *"Subjects.* Seventy-seven patients who underwent TRUS-guided prostatic biopsies on the basis of an abnormal serum PSA (>4ng./ml.) and/or an abnormal digital rectal examination, were **recruited** into the study" [our emphasis].

The urine samples in Clements were not obtained following DRE, but rather following ejaculation, in order to comprise semen.

In view of the above and foregoing, Applicant therefore respectfully suggests that one of ordinary skill in the art would NOT "have been motivated to use male urine" not

containing semen in view of the uncertain teachings of Clements on urine samples which do contain semen.

At page 7, first full paragraph of the OA (as well as at page 9, lines 6 and 14-15), and as alluded above, the Examiner states that "Bussemakers teaches that PSA is *exclusively* expressed in cells of the prostate" [emphasis in the original, at page 7, lines 11-12 of the OA]. In fact that is not the case, as Clements itself teaches at page 1341, left column, third paragraph: "PSA is now known not to be exclusively prostate-specific and is expressed in a wide range of tissues".

The fact that Clements contradicts Bussemakers renders the combination of these two references improper and argues against the motivation to combine them as discussed by the Examiner at the bottom of page 7 (e.g., line 21).

With respect to the allegation at the top of page 5 of the OA that:

> "Clements [sic] *et al* teaches that PSA mRNA expression is intended to be used as a marker for prostate cells when screening patients for markers that are upregulated in patients with prostate cancer (see paragraph flanking pages 1340-1341, in particular) and Bussemakers *et al* teaches PCA3 demonstrates 20-fold overexpression in prostate cancer cells..." [emphasis in the original],

Applicant respectively submits that the Examiner uses a hindsight interpretation of the facts, since Clements, having failed to identify a prostate-cancer specific marker (i.e., PSA and PSM), tried a third marker "Apolipoprotein-D" with the same results. As Clements discussed, in the paragraph flanking pages 1340-1341:

> "since we were unable to discriminate between controls and patients using PSA and PSM, another marker, Apolipoprotein-D, which has been shown by immunostaining to be elevated in prostatic cancers compared with immediately adjacent non-malignant tissue, was used" [our emphasis].

Thus, Apo-D is only used to further assess whether urethral washings following ejaculation, can replace semen samples for molecular diagnostic. Of further note, Clements concludes in the abstract,

> "we have established a sensitive method of detecting prostatic cells in ejaculate and urethral washings and shown that PSA RT-PCR is a reliable indicator of prostate cells in these samples. However, RT-PCR for PSA, PSM and Apolipoprotein-D were not useful for discriminating malignant from non-malignant prostate cells". [our emphasis]

> At the top of page 10, the Examiner states:
>
> "In regards to the argument that the use of urine which does not contain semen is not validated, but rather taught away [the Examiner discussing the Applicant's previous response in the first paragraph of page 20], by Clements..., Applicant is arguing limitations **not** commensurate in scope with the claims. The pending claims do not recite methods where urine 'does **not contain** semen'". [our emphasis]

In view of the amendments to independent claims 41 and 67, which introduce this limitation, Applicant respectfully submits that the allegations of obviousness based on the teachings of Clements alone or together with those of Bussemakers, have been overcome. Applicant also wishes to reiterate on the comment of the Examiner concerning a combination of DRE and the detection of prostate cancer markers (middle of page 10), that Clements does not even hint at obtaining a urine sample which does not contain semen, following a DRE.

Concenling the comment of the Examiner at the bottonl of page 10, Clements does not teach that "PSA RT-PCR is a reliable indicator of prostate cells in urine" that does not contain semen, as discussed above".

In addition, it should be clear from the above, that contrarily to the allegations of the Examiner in the middle of page 11, the combined teachings of Bussemakers and Clements does not teach "the use of mRNA from urine samples [which do not contain

semen] and RT-PCR to detect prostate cells and for assessing the malignant state of the prostate.

With respect to the Examiner's allegation (starting at the bottom of page 11) that the "prior art clearly teaches PCA3 mRNA is differentially expressed in prostate cancer cells found in urine of patients with prostate cancer...(see Example 2 of Bussemakers, in particular)", of course, the Applicant disagrees. Indeed, as also stated by the Examiner at page 4,

> "Bussemakers does not specifically teach methods using a urine sample, a voided urine sample from a patient having an increased number of prostate cells therein, a urine sample containing semen, or a urine sample collected following a digital rectal exam".

Applicant once again reiterates that Bussemakers does not teach or suggest the detection of PCA3 in a urine sample that does not contain semen, together with the detection of a prostate-specific nlRNA.

Finally, with respect to the "reasonable likelihood of success" allegation at page 12, Applicant submits that since (1) PSA is not a marker *"exclusively* expressed in prostate cells"; (2) the detection of PCA3 mRNA and a prostate-specific marker in urine not containing semen had not been validated prior to the present invention; and (3) urine not containing semen was taught away by Clements; that there would not have been a reasonable likelihood of success for the subject matter of the present invention.

In view of the above and foregoing, it should be clear that Clements (alone or together with other cited art) does not suggest the use of urine *per se* as a sample for mRNA detection and prostate cancer diagnosis.

Applicant respectfully submits that, as per §2143.03 of the MPEP, in order "to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art". Since the combination of Bussemakers and Clements

(alone or together with any of the references cited below) does not teach or suggest a method combining the detection of both PCA3 mRNA and a prostate-specific mRNA in a urine sample not containing semen, to determine the presence / absence / predisposition to develop prostate cancer and comprising a determination of an absence of, or a lower risk of developing prostate cancer when in the absence of detection of PCA3, the prostate-specific marker is detected, it does not teach or suggest every element of independent claims 41 and 67.

In view of the above and foregoing, which supports the pioneering nature of the urine-based diagnostic methods claimed, the Examiner is requested to withdraw the obviousness rejection based on the combination of Bussemakers with Clements.

Claims 41-50, 57, 58 and 61-68 are also rejected as being allegedly unpatentable over Bussemakers *et al.,* in view of Clements *et al.,* and in further view of Cheung *et aL,* 1994 (1. Clin. Microbiol., 32:2593-2597) under 35 U.S.C. § 103(a).

Applicant respectfully submits that the teachings of Cheung, concerning the use of silica particles for nucleic acid purification, do not correct the defects of the combination of Bussemakers and Clements in teaching a method combining the detection of both PCA3 RNA and a prostate-specific RNA in a urine sample not containing semen, to determine the presence / absence / predisposition to develop prostate cancer. In view of the above and foregoing, the combination of Bussemakers with Clements and Cheung does not render the claimed nlethods of the invention obvious.

Claims 41-50, 57, 58, 59-63, and 65-69 are also rejected as being allegedly unpatentable over Bussemakers *et al.,* in view of Clements *et al.,* and in further view of Baret (EP 0 256 932 A2).

Applicant respectfully submits that the teachings of Baret concerning chemiluminescent assays do not correct the defects of the combination of Bussemakers and Clements in teaching a method combining the detection of both PCA3 RNA and a prostate-specific RNA in a urine sample not containing semen, to detennine the presence *1* absence *1* predisposition to develop prostate cancer. In view of the above and foregoing, the combination of Bussemakers with Clements and Baret does not render the claimed methods of the invention obvious.

Claims 41-51, 54, 57, 61-63, and 65-68 are also rejected as being allegedly unpatentable over Bussemakers *et al.,* in view of Clements *et al.,* in further view of Buck *et aL,* 1999 (Biotechniques 27(3): 528-536) under 35 U.S.C. § 103(a).

Applicant respectfully submits that the teachings of Buck concerning the design of probes and primers do not correct the defects of the combination of Bussemakers and Clements in teaching a method combining the detection of both PCA3 RNA and a prostate-specific RNA in a urine sample not containing semen, to detennine the presence *1* absence *1* predisposition to develop prostate cancer. In view of the above and foregoing, the combination of Bussemakers with Clements and Buck does not render the claimed methods of the invention obvious.

Claims 41-50, 52, 53, 55, 56, 57, 58, 61-63, and 65-68 are further rejected as being allegedly unpatentable over Bussemakers *et al.,* in view of Clements *et al.,* in further view of Schlegel *et aL,* (US *2002/0168638* A1) under 35 U.S.C. § 103(a).

Applicant respectfully submits that the teachings of Schlegel concerning a large number of markers alleged to be usable in "detecting, characterizing, preventing and treating prostate cancers", and in particular prostate protein markers, do not correct the defects of the combination of Bussemakers and Clements in teaching a method combining the detection of both PCA3 RNA and a prostate-specific RNA in a urine sample not

containing semen, to determine the presence / absence / predisposition to develop prostate cancer. In view of the above and foregoing, the combination of Bussemakers with Clements and Schlegel does not render the claimed methods of the invention obvious.

CONCLUSION

In view of the above and foregoing, it should be clear that the only remaining rejections (under 35 USC § 103(a)) have been overcome by the foregoing amendments and remarks. Applicant therefore believes that the present application is in condition for allowance and prompt and favourable action in this regard is earnestly sollicited. If the Exanliner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Deposit Account Information

Please charge any fees due in connection with this submission, including the fees due under 37 C.F.R. ' 1.17 for a three month extension of time, to Deposit Account No. 07-1742.

Respectfully submitted,

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